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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/731,877	12/09/2003	Jill A. O'Loughlin	B0877.70025US00	9392

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EXAMINER	
FORD, ALLISON M	

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 07/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/731,877	O'LOUGHLIN ET AL.	
	Examiner	Art Unit	
	Allison M. Ford	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5-9,17-24,40,44-46,62,66,67 and 83-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *40,44-46,62,66 and 67* is/are allowed.

6)☒ Claim(s) *1,5-9,17-24 and 86-93* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4)☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: _____.

DETAILED ACTION

Applicants response dated 30 May 2006 has been received and placed into the application file. Claims 1, 40, 62 and 86 have been amended. A declaration by Dr. Lysaght has also been received and fully considered. Claims 1, 2, 5-9, 17-24, 40, 44-46, 62, 66, 67, and 83-93 remain pending in the instant application, all claims have been examined on the merits.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 5-9, 17-21, 86-91 and 93 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Wolfe et al (Int J. Artif. Org, 1987), in view of Ranganathan et al (US 2001/0051150 A1), and in light of The Online Medical Dictionary and IUBMB Enzyme Nomenclature.

Wolfe et al teach an article comprising an oral delivery composition comprising a capsule, the capsule comprising isolated urease dissolved in a 10% haemoglobin solution (which applicant calls a pharmaceutically acceptable carrier) and a zirconium phosphate material (an ammonium uptake species) (See Wolfe et al, Pg. 269, col. 2-Pg. 270, col. 1) (Claims 2, 18-21, 88 & 92). Wolfe et al does not include any whole cells in their composition (Claim 17). Wolfe et al teach that the urease successfully breaks down urea in gut fluid, and the zirconium phosphate helps to absorb ammonium produced as a bi-product of the urea breakdown (See Wolfe et al, abstract). Wolfe et al teach the orally ingestible article is intended to remove urea in patients with kidney failure in order to delay the need of dialysis therapy or to reduce dialysis treatment times (See Wolfe et al, abstract).

Wolfe et al only teaches inclusion of urease enzymes for breakdown of urea in patients with kidney failure; however it would have been obvious to one of ordinary skill in the art at the time the invention was made to additionally include appropriate enzymes for the enzymatic breakdown of additional toxins known to build up in patients with kidney failure, specifically uricase and creatininase, for the breakdown of uric acid and creatinine, respectively (See Online Medical Dictionary "Uricase" and IUBMB Enzyme Nomenclature "EC 3.5.2.10") (Claims 1, 86, 87, 89, and 90). At the time the invention was made it was well known that several nitrogenous wastes build up in the systems of kidney failure patients, most notably urea, uric acid and creatinine (See Ranganathan et al, Pg. 1, paragraph 0005 & Pg. 2, paragraph 0012). For the most effective treatment all three of the nitrogenous wastes should be removed from the intestines of the individual (See Ranganathan et al, Pg. 2 paragraph 0012). One of ordinary skill in the art would have been motivated to include isolated uricase and creatininase in the microcapsules of Wolfe et al, along with the urease, for the effective breakdown of uric acid, and creatinine and urea, respectively, in a patient suffering renal failure because the most effective treatment requires removal of all three toxins present in elevated concentrations in the gastrointestinal tract of such patients (See Ranganathan et al, Pg. 1, paragraph 0005). One would expect success including isolated uricase and creatininase in the microcapsules of Wolfe et al because uricase and creatininase are both commercially available, and one would not expect negative interactions between the three enzymes within the microcapsule; rather one would have a reasonable expectation that the uricase and creatininase would function similarly to the urease by breaking down their respective toxins.

Additionally, though Wolfe et al teach the urease enzymes are encapsulated, they are relatively silent on the specifics of the actual capsule. However, Ranganathan et al teach a microcapsule carrier for oral ingestion wherein the actual microcapsule can be designed to be insusceptible to acid degradation, so that the contents of the capsule are not substantially released externally from the capsule, can be enterically coated, and wherein the capsule does not impede mass transport of uric acid or creatinine

through the capsule; material suitable for such microcapsules include alginate (See Ranganathan et al, Pgs. 2-3, paragraph 0020). Therefore, at the time the invention was made it would have been well within the purview of one of ordinary skill in the art to use a capsule material, such as that described by Ranganathan et al, in the microcapsules of Wolfe et al, modified to additionally contain isolated uricase and creatininase enzymes (Claims 5-9, 91 and 93). One of ordinary skill in the art would have been motivated to use a microcapsule such as that described by Ranganathan et al, to encapsulate the enzymes of Wolfe et al, in order to protect the urease from proteolytic enzymes in the gut (See Wolfe et al, Pg. 269, col. 2), to ensure the article is delivered to the intestines, where maximal degradation of the urea is to occur, as opposed to being degraded in the acidic stomach environment, and in order to contain the active enzymes in a protected capsule where they are protected from binding of other macromolecules present in the gut that may inhibit the enzymatic action. One would expect success using the microcapsule of Ranganathan et al because Ranganathan et al teach their microcapsules can successfully be ingested and are delivered to the intestines of the individual without substantially being degraded by acid or releasing their contents externally of the capsule (See Ranganathan et al, Pg. 3, paragraph 0020). Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 18-24 and 92 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Wolfe et al (Int J. Artif. Org, 1987), in view of Ranganathan et al (US 2001/0051150 A1), and further in view of Kominami et al (US Patent 4,240,376), Sparks et al (Trans Am. Soc. Artif. Int Organs, 1972) and Smith et al (US Patent 4,857,555).

Wolfe et al teach an article comprising an oral delivery composition comprising a capsule, the capsule comprising isolated urease dissolved in a 10% haemoglobin solution (which applicant calls a pharmaceutically acceptable carrier) and a zirconium phosphate material (an ammonium uptake species) (See Wolfe et al, Pg. 269, col. 2-Pg. 270, col. 1). Wolfe et al teach that the urease successfully breaks

down urea in gut fluid, and the zirconium phosphate helps to absorb ammonium produced as a bi-product of the urea breakdown (See Wolfe et al, abstract). Though Wolfe et al only includes urease in their composition, it would have been obvious to one of ordinary skill in the art at the time the invention was made to additionally include isolated creatininase and uricase, see teachings above.

Wolfe et al does teach inclusion of a zirconium phosphate as an ammonium uptake species; however, it would have been obvious to one of ordinary skill in the art to alternatively use activated carbon (See Kominami et al, col. 5, ln 51-66) or oxidized starch (which applicant calls oxystarch) (See Sparks et al, Pg. 459) (Claims 18-21 & 92). Like Wolfe et al, Kominami et al and Sparks et al have all shown activated carbon and oxidized starch to be suitable sorbents for the adsorption of ammonia, which is formed by the breakdown of urea by urease. Therefore one of ordinary skill in the art would have been motivated to alternatively use activated carbon or oxidized starch in place of the zirconium phosphate as the ammonium uptake species, and would have expected success in doing so, as they are functional equivalents.

Other known ammonium uptake species include a glutamine synthetase. Smith et al teach that glutamine synthetase is responsible for catalyzing the synthesis of glutamine from glutamate and ammonia (See Smith et al, col. 1, ln 34-50); the glutamine produced by this reaction is readily used by the body in a variety of natural ways. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to alternatively include glutamine synthetase in the modified microcapsule of Wolfe et al in place of the zirconium phosphate (Claims 22-24 and 92). One would have been motivated to substitute glutamine synthetase in the modified microcapsule of Wolfe et al in place of the zirconium phosphate as the ammonium uptake species as they are functional equivalents. One would have expected success because Smith et al teach that glutamine synthetase catalyzes the reaction of glutamate and ammonia to form glutamine, which can then forth be utilized directly in the gastrointestinal tract as respiratory fuel (See Smith et al, col. 1, ln 34-col. 2, ln 2).

Therefore the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments filed 30 May 2006, as well as the declaration of Dr. Lysaght, have been fully considered, and are found persuasive, in part.

With regards to independent claims 1 and 86, and dependent claims thereof, applicants argue that there would not have been a reasonable expectation of success for the proposed combination of teachings of Wolfe et al and Ranganathan et al. Specifically, applicants argue Wolfe et al only teaches an artificial *in vitro* system, which they assert has no relevance to *in vivo* systems. Applicants argue that Wolfe et al actually teach away from use *in vivo*. Thus applicants feel that because the system of Wolfe et al does not predict an *in vivo* system, there would be no motivation to modify the teachings of Wolfe et al in view of Ranganathan, as asserted by the examiner, to arrive at the instant invention, and even if the system of Wolfe et al was modified, there would be no reasonable expectation that the modified system would work *in vivo*. Applicants further present an argument that the composition of Wolfe et al does not encapsulate zirconium phosphate, but leaves it free, whereas Ranganathan teaches encapsulating the sorbent; applicants argue that because of this difference it is not clear how one would even combine Wolfe et al and Ranganathan. Regarding the tertiary references Kominami, Sparks et al, and Smith et al, applicants argue that none of these references cure the deficiencies discussed above, and thus do not anticipate the independent claims, much less the dependent claims.

These arguments are not found persuasive. First it is noted that the claims are directed to a product composition, not a method of treatment; therefore, applicants arguments that one of ordinary skill in the art would not have a reasonable expectation that the modified system of Wolfe et al (modified to comprise additional uremic enzymes) would function *in vivo* are not applicable. Rather, it is only

required that one of ordinary skill in the art would have a reasonable expectation of successfully modifying the product of Wolfe et al to comprise additional isolated uremic enzymes. Because isolated uricase and creatininase are commercially available, and means are known to encapsulate isolated enzymes (i.e. See Wolfe et al), the examiner maintains that one of ordinary skill in the art would have a reasonable expectation of successfully modifying the product of Wolfe et al to achieve the instant invention.

It is, however, recognized, that in order for one of ordinary skill in the to have been motivated to modify the product of Wolfe et al in the proposed manner, there would have to be a reasonable expectation that encapsulated uremic enzymes would function to reduce uremic toxin levels *in vivo*. However, contrary to applicants assertions regarding the inability of the system of Wolfe et al to function *in vivo*, the mere lack of *in vivo* working examples is not sufficient to show that the system of Wolfe et al is non-operative *in vivo,* and does not amount to a teaching away from use *in vivo*.

Though Wolfe et al does not test their product *in vivo*, Wolfe et al does suggest that the artificial *in vitro* test conditions do correlate to *in vivo* systems, and thus it is feasible to extrapolate the results found *in vitro* to *in vivo* applications. It is recognized that Wolfe et al does admit that the degree of efficacy of their product may vary in *in vivo* ("The first question to ask is whether a gut urea clearance of 3 ml/min can really be attained *in vivo* with this system. The definite answer cannot be given here." See Wolfe, pg 273, 2nd col.), however, despite a concrete evidence regarding the degree of efficacy, Wolfe et al do suggest that the product is effective, to some degree, *in vivo* ("What can be concluded is that the systems efficacy is not at all decreased in gut fluid and therefore is potentially useful in oral therapy." See Wolfe, pg 273, 2nd col.). Therefore, there is a suggestion in Wolfe that their product system would be useful for *in vivo* therapy; the lack of working examples *in vivo* is not sufficient to show non-enablement of the product system of Wolfe in *in vivo* applications.

Thus, one of ordinary skill in the art would have had a reasonable expectation that the system of Wolfe et al would function to lower urea levels *in vivo*, based on the *in vitro* experiments presented by Wolfe et al. And thus, one would have been motivated, as proposed above, to modify the system of Wolfe et al to contain additional uremic enzyme uricase and creatininase.

Second, regarding applicants argument that based on the differences between the products of Wolfe et al and Ranganathan, it is not clear how one of ordinary skill in the art would be able to even combine Wolfe and Ranganathan, it is noted that the product of Ranganathan was not relied upon, rather only their teachings regarding the build up of all three of urea, uric acid and creatinine in the gastrointestinal tract of uremic patients and the need for removal of all three toxins for the most effective treatment (See Ranganathan et al, Pg. 1, paragraph 0005 & Pg. 2, paragraph 0012) were relied upon. Therefore, applicants arguments are not persuasive because they are not related to the subject matter relied upon in the rejection, as the examiner never asserted the combination of the products of Wolfe et al and Ranganathan.

Third, regarding the tertiary references Kominami, Sparks et al and Smith et al, it is noted that none of the tertiary references anticipate or render obvious the invention of the independent claims; rather these references were relied upon for their teachings regarding use of different ammonium uptake species. If applicants can show the independent claims are non-obvious over the primary reference (Wolfe et al) and secondary reference (Ranganathan) the rejections of the dependent claims will be obviate as well.

With regards to independent claims 40 and 62, and dependents thereof, applicants argue that the examiner relied on impermissible hindsight to conclude that one would have had a reasonable expectation of success. Specifically, applicants argue that the mechanism by which the *E. coli* DH5 express and

secrete the urease is not disclosed by Chang et al (for example, it is unknown if (i) the urease remains inside the cell, and the urea must penetrate into the cell and be degraded intracellularly; if (ii) the urease is secreted outside the cell, but remains inside the boundaries of the microcapsule, in which case the urea must penetrate the microcapsule to be degraded; or if (iii) the urease is secreted outside the cell and is released externally of the capsule, in which case the urea can be degraded in the gut environment); because the mechanism/location of the urea degradation by urease is not known, applicant argue it is improper for the examiner to assert that uricase and/or creatininase expressed by a transfected cell, would function in an equivalent manner. Urea is a smaller molecule than either uric acid or creatine, thus if urea needs to penetrate into the microcapsule or into the cell, there is no evidence the same degree of penetration would be possible with uric acid or creatine. The declaration by Dr. Lysaght supports this stance that, based on the limited disclosure of Chang et al, one of ordinary skill in the art would not be able to reasonably expect an equal level of success in degrading uric acid and creatine by using *E.coli* transfected with those genes.

These arguments are found persuasive. The examiner concedes that Chang et al does not teach if the urease is maintained intracellularly or secreted extracellularly, and if the latter, if it is released externally from the microcapsule; therefore, it is unknown how and where the degradation of urea takes place. Because it is unknown how and where the degradation of urea takes place, it is improper to assume that uric acid and creatine can successfully be degraded in a similar manner.

It is noted that the claims are directed to a product, not a process of treatment, and while the examiner maintains that one of ordinary skill in the art would have had a reasonable expectation of successfully modifying the product of Chang et al to comprise cells transfected with one or more of uricase, urease and creatininase, it is conceded that there was a lack of *motivation* to modify the product as proposed. One would not be motivated to modify the product of Chang et al as proposed because there is no teaching or suggestion in the art that uricase or creatininase, if expressed by *E.coli* (or other bacteria)

would be able to successfully degrade uricase and creatine in the gut of an uremic patient, respectively, as the mechanism and site of degradation was not clear. Because the molecules of uric acid and creatine are unique from urea, as well as from one another, it cannot be assumed, in the lack of evidence, that they would be degraded in the same manner as urea. Therefore, because one would not have had a reasonable expectation that the product would have worked successfully, there would not be a motivated to perform the modification as suggested.

Claims 40,44-46,62,66 and 67 are considered to be in condition for allowance.

Claims 1, 5-9, 17-24 and 86-93 remain rejected for the reasons of record.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Allison M. Ford whose telephone number is 571-272-2936. The examiner can normally be reached on 7:30-5 M-Th, alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Allison M Ford
Examiner
Art Unit 1651